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(54) **Composition comprising a hydrophilic polymer and a hydrophilic material different therefrom**

(57) A composition capable of being formed into articles having substantial dimensional stability and improved dissolution characteristics, which composition comprises a medium and a phase, the medium functioning as a dispersion medium with respect to the phase, the phase functioning as a disperse phase with respect to the medium, the phase being present in the composition at a concentration sufficient to effect an increase in dissolution of articles in comparison with the rate of dissolution of articles made from a composition absent the phase, the medium consisting of a solidified hydrophilic polymer and the phase comprising at least one hydrophilic material which is substantially insoluble in the medium comprising the hydrophilic polymer.

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Composition comprising a hydrophilic polymer  
and a hydrophilic material different therefrom  
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The present invention relates to compositions comprising a dispersion medium consisting of a melt comprising a hydrophilic polymer, and a disperse phase comprising at least one hydrophilic, preferably hygroscopic, material different therefrom, said compositions having improved dissolution characteristics. The terms hydrophilic polymer, dispersion medium, disperse phase, hydrophilic material and hygroscopic material are defined hereinafter.

It is known that many hydrophilic polymers, which in the dry state (i.e. in the absence of water) cannot be melted and decompose at an elevated temperature, form a thermoplastic melt in the presence of a defined amount of water. An example of such a hydrophilic polymer is gelatin. It is also known that hydrophilic polymers that do melt in the dry state at elevated temperature form thermoplastic melts at those temperatures also in the presence of defined amounts of water.

Such hydrophilic polymers can be treated at an elevated temperature to form a melt. The process is conveniently carried out in an injection moulding machine or extruder. The hydrophilic polymer is fed through the hopper onto a rotating, reciprocating screw. The feed material moves along the screw towards the tip. During this process, its temperature is increased by means of external heaters around the outside of the barrel and by the shearing action of the screw. Starting in the feed zone and continuing in the compression zone, the particulate feed becomes gradually molten. It is then conveyed through the metering zone, where homogenization of the melt occurs, to the end of the screw. The molten material at the tip can then be further treated by

injection moulding or extrusion or any other known technique to treat thermoplastic melts, to obtain shaped articles.

This treatment is described in the European Patent Application No. 83 301 643.9 (Publication No. 0 090 600) which is incorporated herein by reference.

The preferred hydrophilic polymers of the present invention are natural hydrophilic polymers and especially gelatin. Such gelatin is made preferably from acid or alkaline processed ossein, acid processed pigskin, or alkaline processed cattle hide. Said types of various gelatin have a molar mass range of 10,000 to 2,000,000 grammes per mole (g/mol) or a molar mass range of 10,000 to 2,000,000 and 10,000,000 to 20,000,000 g/mol. Such gelatins are known.

However, other hydrophilic polymers as described herein are included in this invention. Hydrophilic polymers are polymers with molar masses from approximately  $10^3$  to  $10^7$  g/mol carrying functional groups in their backbone and/or in their side-chains which are capable of participating in hydrogen bonding. Such hydrophilic polymers exhibit in their water absorption isotherm in the temperature range between approximately 0 to 200°C an inflection point close to the water activity point at 0.5.

Articles made from such hydrophilic polymer melts are useful for many applications. An important property is the capability of such articles to take up water and to disintegrate.

For many purposes the speed of disintegration must be high, which, for example, is the case for pharmaceutical containers. Pharmaceutical containers in the form of conventional hard gelatin capsules made by the known dip moulding process generally have a dissolution time which is somewhat shorter than that for similar containers but made by an injection moulding process. It is, therefore, an object of the present invention to reduce the dissolution time of such injection moulded capsules.

According to the present invention there is provided a composition . . . capable of being formed into articles having substantial dimensional stability and improved dissolution characteristics, comprising a medium and a phase, the medium functioning as a dispersion medium with respect to the phase, the phase . . . functioning as a disperse phase with respect to the medium, the phase being present in the composition at a concentration sufficient to effect an increase in dissolution of articles in comparison with the rate of dissolution of articles made from a composition absent said phase, the medium comprising a solidified hydrophilic polymer and the phase comprising at least one hydrophilic material which is substantially insoluble in the medium forming the hydrophilic polymer.

This composition may be in the form of a powdery mixture of its components or in the form of a melt or in a solidified form as obtainable from such a melt, for example, in the form of solid particles such as granulates, pellets or powders. These forms of the novel compositions are primarily useful themselves for making finished articles according to the present invention. Said powdery mixtures or said solidified forms may be processed into a melt from which finished articles may be formed.

The invention particularly provides shaped articles as obtained from the composition, which articles are selected from the group consisting of bottles, sheets, films, packaging materials, pipes, rods, laminated films, sacks, bags, foams, granules, powders, and pharmaceutical containers.

The invention further provides shaped articles as above when used as a carrier material comprising a member selected from pharmaceutically and veterinarianily active compounds.

The invention still further provides a process for producing a composition . . . capable of being formed into articles having substantial dimensional stability and improved dissolution

characteristics, which composition comprises a medium and a phase, the medium functioning as a dispersion medium with respect to the phase, the phase functioning as a disperse phase with respect to the medium, the phase being present in the composition at a concentration sufficient to effect an increase in dissolution of articles in comparison with the rate of dissolution of articles made from a composition absent the phase, the medium comprising of a solidified hydrophilic polymer and the phase comprising at least one hydrophilic material which is substantially insoluble in the medium forming hydrophilic polymer, which process comprises heating said hydrophilic polymer to a temperature above the melting point and glass transition temperature of the hydrophilic polymer for a time sufficient to effect melt formation, characterised in that the material which functions as the disperse phase is added to the hydrophilic polymer either before, during or after melt formation.

The invention still further provides a process of shaping the composition to form shaped articles, which process is selected from injection moulding, blow moulding, extrusion, co-extrusion, compression moulding, vacuum forming, foaming and thermoforming.

The disperse phase is preferably comprised by a fibrous polymer selected from polysaccharides, preferably from the group consisting of cellulose, chitin, starch, or chitosan which preferably are cross linked and wherein some of the hydroxyl groups of the constituent anhydro-glucose units are substituted. Alternatively, the disperse phase may be a polyvinylpyrrolidone polymer.

Such fibrous polymers have been added to gelatin in the dip moulding process for the production of hard gelatin capsules in a concentration of up to 10%. However, no increase in the dissolution rate of capsules so produced was noticed, when compared to like capsules but made in the absence of said fibrous polymers.

It was therefore surprising to find that, although the mixture according to the present invention undergoes melt formation in the presence of water at elevated temperatures and pressures, when present at low concentrations such fibrous polymers enhance the dissolution characteristics of the solidified melt.

The invention will be further apparent from the following description with reference to the accompanying examples.

The terms "dispersion medium" and "disperse phase" within the context of the invention are to be construed in accord with the following: The composition of the present invention consists of material comprised by a medium and material comprised by a phase. It is a requirement of the present invention that the medium be incompletely miscible with the phase when both are present in the composition, i.e., that the phase is dispersed in, but not dissolved in, the material comprising the dispersion medium. The phase may thus include course particles or particles of smaller size to form colloidal systems, or larger particles when such behave likewise when present in the thermoplastic melt.

The term "hydrophilic material" within the context of the invention means a material which is water-soluble and water swellable, i.e. a material which is able to take up water at room temperature in an amount of at least 10 grams per 100 grams of material, and preferably in an amount of at least 20 grams per 100 grams of material.

The term "hygroscopic material" within the context of the invention is to be construed in accord with the following: A hygroscopic material is one which readily absorbs and/or absorbs and retains moisture from the environment at room temperature, but does not liquify due to dissolution of said material by absorption, adsorption and retention of the moisture. Such material may adsorb and/or absorb and retain water at a rate of up to 1000 times its own weight.

The term "hydrophilic polymer" as defined above includes the following, insofar as they do not form a disperse phase, within the context of this invention: substantially water-soluble polymers, for example animal gelatin, vegetable gelatins, proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, rape seed proteins, acrylated proteins; substantially water-soluble polysaccharides, alkylstarches, hydroxyalkyl starches and hydroxyalkylalkyl starches, such as: methylstarch, hydroxymethylstarch, hydroxyethyl starch, hydroxypropyl starch, hydroxyethylmethyl starch, hydroxypropylmethyl starch, hydroxybutylmethyl starch, starch esters and hydroxyalkyl starch esters such as: starch acetatephthalate, Hydroxypropylmethyl-starch phthalate; carboxyalkylstarches, carboxyalkylalkylstarches; alkylcelluloses, hydroxyalkyl celluloses and hydroxyalkylalkyl celluloses, such as: methylcellulose, hydroxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose, hydroxybutylmethyl cellulose, cellulose esters and hydroxyalkyl cellulose esters such as: cellulose acetatephthalate (CAP), Hydroxypropylmethyl cellulose phthalate (HPMCP); carboxyalkylcelluloses, carboxyalkylalkylcelluloses; esters such as carboxymethylcellulose and their alkali metal salts, water-soluble synthetic polymers such as: polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinyl alcohols, polyvinyl acetatephthalates (PVAP), polycrotonic acids; polyitaconic acid, polymaleic acid; suitable are also phthalated gelatin, crosslinked gelatin, shellac, gelatin succinate, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; and other similar polymers insofar they are essentially water-soluble.

The term "hydrophilic polymer" within the context of this invention means a polymer which is essentially water-soluble, i.e. it is able to take up water at a rate of at least 50 grams

of water per 100 grams of the polymer at room temperature.

If the hydrophilic polymer is not gelatin and only admixed to the gelatin, it is sufficient that said hydrophilic polymer is only "water-swellable", i.e. it takes up at least 10 grams of water per 100 grams of the polymer at room temperature. Such an admixed hydrophilic polymer, must, however, not form a separate phase from the gelatin. Of course, it is possible to use also a mixture of these polymers.

Preferred is gelatin as defined above and gelatin as occurs in its partial salt form, and as is used in the dip moulding of hard gelatin capsules. If other hydrophilic polymers are mixed with gelatin these may be mixed in any desired ratio. Preferably gelatin is present in an amount of at least 50 %, preferably in an amount of at least 70 % and most preferably in an amount of at least 90 % by weight of the total composition.

If other essentially water-soluble polymers are admixed to the gelatin, then synthetic polymers are preferred such as polyacrylic acids, polyacrylic acid esters, polymethacrylic acids, polymethacrylic acid esters, polyvinyl alcohols.

Such other hydrophilic polymers as mentioned may optionally be added in any desired amount preferably in an amount up to 50 %, preferably up to 30 % and most preferably within a ratio of gelatin: other hydrophilic polymer of 90 - 97 : 10 - 3 % by weight calculated to the dry components of the composition.

The water content of such a hydrophilic polymer/water composition is about 1 - 40% water by weight of the total composition and preferably about 5 - 25 %. However, in order to work with the material near its equilibrium water content to which it gets when it is finally exposed to the free atmosphere, a water content of 8 - 20 %, preferably of 10 - 16 % by weight calculated to the total composition should preferably be used in processing. If, for example, the gelatin contains only 1 % to 8 % of water it may



be advisable to add some plasticizer in order to ease processing. This should be done in an analogous manner for the other hydrophilic polymers.

For such hydrophilic polymers which are not gelatin the water content may be lower than the water content generally indicated above as is the case for several of the cellulose derivatives. However, this is merely an experimental optimization which can easily be carried out by one skilled in the art.

The hydrophilic material of the disperse phase has a melting point which preferably is higher than the glass transition temperature of the hydrophilic polymer and preferably absorbs up to a thousand times its own weight in water. The precise amounts of water absorbed by the material vary according to its nature and the ionic strength of the aqueous environment in which it is situated. For example, the amount of water absorbed is generally reduced as ionic strength is increased.

The material comprises a polymer of glucose moieties, and preferably is selected from the group consisting of cellulose, chitin, starch and chitosan.

Preferably, at least some of the hydroxyl groups of anhydroglucose moieties comprised by the polymer are substituted, with, for example, a member from the group consisting of carboxy-carboxyalkyl, sulfoalkyl, and salts thereof, and dialkylaminoalkyl, - or quaternary derivative thereof. Such derivatives are, for example, carboxymethylcellulose, diethylaminoethyl cellulose, triethanolamine cellulose, polyethyleneimine cellulose, and carboxymethyl starch.

In the preferred embodiment, the disperse phase is comprised by the compounds mentioned above, which are internally cross linked. These polymers are preferably substituted to a degree of between 0.5 and 1.2 and preferably are substituted to a degree of about 0.7. Preferably such materials are of a strand or fibrous type,

and have an average strand or average fibre length of from about 10 to about 500um. More preferred such average strand or fibre sizes are from about 20 to about 300um, and most preferred such sizes are from about 20 to about 100um. Said materials are preferably cross linked to such an extent that they are substantially water-insoluble. Preferred cross linked materials include cross-linked carboxymethyl starch, internally cross-linked carboxymethyl cellulose and salts thereof, and cross-linked cellulose amines possessing tertiary or quaternary amino groups.

Internally cross linked sodium carboxymethyl cellulose is listed in the US-National Formulary as Croscarmellose Sodium Type A as sold by FMC Corporation (Philadelphia, USA) under the Trade name Ac-Di-Sol. The average strand or fibre size of said cross-linked carboxymethyl cellulose is from about 70 to about 80um, and it has been used previously at concentrations of between 2 and 6% as a disintegrant in tablets and capsules made by a dry cold compression process. A molten system comprising a water-containing hydrophilic polymer melt, where generally temperatures of between 90 and 180°C as well as high pressures are used is considerably different from a conventional pharmaceutical tablet manufactured at room temperature using substantially dry materials.

Chemically modified suitable starches comprised by the material, such as carboxymethyl starch or sodium starch glycolate are available under the Trade names of Explotab (Edward Mendell Company Incorporated Carmel, New York) and Primojel (Generichem Corp. Little Falls, New Jersey). The average fibre or strand size of said modified starches is about 70um.

A further material suitable as the hydrophilic material of the disperse phase is microcrystalline cellulose as sold under the trade name Avicel PH-101 by Fluka Chemie AG of Industriestrasse 25, CH-9470 Buchs, Switzerland. The average fibre or strand size of said microcrystalline cellulose is from about 20 to about

100um, depending upon the grade used.

A still further material suitable as the hydrophilic material of the disperse phase is a cross linked polyvinylpyrrolidone as sold under the Trade name Polyplasdone XL (GAF Corp., New York), or Kollidon. The average fibre or strand size of said polyvinylpyrrolidone depends on the precise grade used, but is typically in the range of from about 20 to about 250um.

Pullulan, or pullulan derivatives, which are, or are rendered substantially insoluble in the hydrophilic polymer, by cross linking or acetylation, for example, may be used as the hydrophilic material of the disperse phase.

The pullulan or derivative may be substituted to between about 0.5 and 1.0.

The hydrophilic material is present in the thermoplastic melt at a concentration of between about 0.1 and 4%, by weight, based on the weight of the thermoplastic melt. Preferably the material is present in the thermoplastic melt at a lower concentration of between about 0.3 and about 2%, by weight, based on the weight of the thermoplastic melt, and most preferably is present in the thermoplastic melt at a concentration of between about 0.5 and about 1.5%, by weight, based on the weight of the thermoplastic melt.

The hydrophilic polymer may be mixed with the material of the disperse phase, and optionally other additives as mentioned herein, in any desired sequence. For example the hydrophilic polymer may be mixed with all the additives including the material and then heated for deconstructurization to form a melt.

The granular size of the starting material is not critical and it can be processed in standard equipment which is commercially available.

The hydrophilic polymer may also be mixed with optional additives, destructure and granulated first and then mixed with the hydrophilic material of the disperse phase for further processing.

The hydrophilic polymer is preferably mixed with the additives as named herein together with the material to yield a free flowing powder useful for continuous processing and destructure and either granulated or directly moulded into a shaped article, e.g. a pharmaceutical container.

Thus, the hydrophilic polymer and all the additives can be mixed in a conventional mixer, the water content of the hydrophilic polymer being within the range as mentioned above. This mixture can then be passed through an extruder to produce granulates or pellets as one form of shaped articles useful for further processing. However, it is possible to avoid granulating and to process the obtained melt directly using down-stream equipment to produce pharmaceutical capsules, other containers, films, blown films included, sheets, profiles, pipes, tubes, foams or other shaped articles. The sheets can be used for thermoforming.

In order to form a melt of the new polymeric composition according to this invention, it is suitably heated in a screw and barrel of an extruder for a time long enough to effect destructure and melt formation. Depending on the amount and types of additives the temperature is preferably within the range of 50°C to 180°C, preferably within the range of 80°C to 130°C also of course depending on the type of hydrophilic polymer used. For this melt formation, the composition is heated preferably in a closed volume. A closed volume can be a closed vessel or the volume created by the sealing action of the unmolten feed material as happens in the screw and barrel of injection moulding or extrusion equipment. In this sense the screw and barrel of an injection moulding machine or an extruder is to be understood as being a closed vessel. Pressures created in a closed vessel correspond to the vapour pressure of water at the used

temperature but of course pressure may be applied and/or generated as normally occurs in a screw and barrel. The preferred applied and/or generated pressures are in the range of pressures which occur in extrusion and are known per se, for example from up to about  $150 \times 10^5 \text{ N/m}^2$ , preferably up to about  $75 \times 10^5 \text{ N/m}^2$  and most particularly from about 5 to about  $50 \times 10^5 \text{ N/m}^2$ . The obtained destructureized hydrophilic polymer composition is granulated and ready to be mixed with the further components according to a chosen mixing and processing procedure to obtain the granular mixture of the starting material to be fed to the screw barrel.

However, the obtained melt in the screw and barrel may be processed further directly, e.g. injection moulded directly into a suitable mould, i.e. directly further processed to a final product if all necessary components are already present.

Within the screw, the granular mixture is heated to a temperature which is generally within the range of about  $50^\circ\text{C}$  to  $180^\circ\text{C}$ , preferably within the range of about  $80^\circ\text{C}$  to  $130^\circ\text{C}$ .

The minimum pressures applied under which the melts are formed correspond to the water vapour pressures produced at said temperatures. The process is carried out in a closed volume as explained above, i.e. in the range of the pressures which occur in extrusion as mentioned above or in the range of pressures used in injection moulding.

When forming a shaped article by extrusion the pressures are preferably as mentioned above. If the melt according to this invention is injection moulded, for example, the normal range of injection pressures used in injection moulding is applied, namely from about  $100 \times 10^5 \text{ N/m}^2$  to about  $3,000 \times 10^5 \text{ N/m}^2$  and preferably from about  $400 \times 10^5$  to about  $2,200 \times 10^5 \text{ N/m}^2$ .

The hydrophilic polymer of the present invention used as starting material may be mixed with the different known additives e.g.

fillers, mould release agents, plasticizers, stabilizers and/or colouring agents.

Examples of fillers are inorganic fillers, such as the oxides of magnesium, aluminum, silicon, titanium, etc. calcium carbonate, preferably in a concentration in the range of about 1 to 50 % by weight, preferably about 2 to about 10 % based on the total weight of all the components. Other known fillers may be used.

Examples of lubricants are stearates of aluminum, calcium, magnesium and tin as well as magnesium silicate, silicones, etc. which may be present in concentrations of about 0.1 to about 5 % preferably at about 0.1 - about 3 % based upon the weight of the total composition.

Examples of plasticizers include low molecular poly(alkylene oxides), such as poly(ethylene glycols), poly(propylene glycols), poly(ethylene-propylene glycols); organic plasticizers of low molar masses, such as glycerol, pentaerythritol, glycerol monoacetate, diacetate or triacetate; propylene glycol, sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, etc., added in concentrations ranging from about 0.5 to about 25 %, preferably ranging from about 0.5 to about 10 % based on the total weight of all the components.

Examples of colouring agents include known azo dyes, organic or inorganic pigments, or colouring agents of natural origin. Inorganic pigments are preferred, such as the oxides of iron or titanium, these oxides, known per se, being added in concentrations ranging from about 0.001 to about 10 %, preferably about 0.5 to about 3 %, based on the weight of all the components.

The sum of the plasticizer and water contents within the hydrophilic component should preferably not exceed the values given for the water content, i.e. about 40 %, and should most preferably not exceed about 30 %, based on the weight of the

composition resp. the preferred values for the water content as given above. It will be obvious to those skilled in the art to determine the optimum water and plasticiser content for the different hydrophilic polymeric materials.

The materials may further contain stabilizers, such as antioxidants and antimicrobial agents.

The materials described herein above form thermoplastic melts on heating and in a closed volume, i.e. under conditions of controlled water-content and pressure. Such melts can be processed like conventional thermoplastic materials, using, for example, injection moulding, blow moulding, extrusion and coextrusion (rod, pipe and film extrusion), and compression moulding, to produce known articles. The articles include bottles, sheets, films, packaging materials, pipes, rods, laminated films, sacks, bags, foams, pharmaceutical capsules, granules or powders. Preferred is the shape of a pharmaceutical carrier (capsule) made by injection moulding.

Such blended materials may be used also as carrier materials for active substances, and may be mixed with active ingredients such as pharmaceuticals and/or agriculturally active compounds such as insecticides or pesticides for subsequent release applications of these ingredients. The resulting extruded materials can be granulated or worked to fine powders.

The following examples further explain the invention.

#### Example 1

100 parts of a commercial gelatin of 240 Bloom adapted to a water content of 17 % by weight are intensively mixed with 2 parts Ca-Stearate per 100 parts of gelatin and different concentrations (see below) of the disperse phase material Croscarmellose sodium, in the form of a dry powder so that a freely flowing granulate is obtained. The concentrations of Croscarmellose sodium used

are 1 part per 100 parts of gelatin, 2 parts per 100 parts of gelatin, and 3 parts per 100 parts of gelatin.

The thus produced granulates are then filled into the hopper of a screw-injection moulding machine, equipped with an 18 mm screw (L/D ratio: length over diameter ratio: 25, Arburg Allrounder 220-90-350). The processing conditions of this injection moulding experiment are as follows:

Barrel Temperature profile:

$T_b$ : 90°C /  $T_m$ : 125°C /  $T_e$ : 150°C /  $T_g$ : 150°C

Screw speed: 160 [rpm]

Injection time: 0.2 seconds

Cycle time: 5 seconds

The injection pressures vary from about 2000 bar for the granulate containing no added Croscarmellose to about 2200 bar for the granulate containing 3 parts Croscarmellose per 100 parts gelatin.

The various gelatin compositions are moulded into capsule cap and body parts using a mould with four cavities.

Under these conditions, gelatin capsules of good quality are obtained under continuous processing - the capsule parts thus obtained are not soft and keep their shape unchanged upon storage.

The capsule containers were filled with identical formulations of paracetamol powder comprising 85.4 parts paracetamol, 2.5 parts of maize starch, 11.7 parts of microcrystalline cellulose (Avicel) and 0.26 parts of hydrogenated cottonseed oil. The

containers were filled with the paracetamol formulation using a Bosch filling machine.

The dissolution rates of paracetamol from the samples are



determined using the standard USP test procedure for paracetamol capsules. The results of the determination are given in Table 1.

Table 1

	% Paracetamol dissolved after		
	15min	30min	45min
CAPSULE without disperse phase	61	84	94
CAPSULE with 1.0% Croscarmellose sodium as disperse phase	62	91	95
CAPSULE with 2.0% Croscarmellose sodium as disperse phase	72	98	100

Example 2

100 parts of a commercial gelatin of 240 Bloom adapted to a content of 17 % by weight of water is intensively mixed with 0.8 parts of a disperse phase material in the form of a dry powder so that a freely flowing granulate is obtained.

The disperse phase materials are (a) Croscarmellose sodium, (b) cross linked polyvinylpyrrolidone, (c) carboxymethyl cellulose, (d) carboxymethyl starch, and (e) microcrystalline cellulose (Avicel).

The thus produced granulates are then filled into the hopper of a screw-injection moulding machine, equipped with an 22 mm screw (L/D ratio: length over diameter ratio: 21, Arburg Allrounder 220-90-350). The processing conditions of this injection moulding experiment are as follows:

Barrel temperature profile:

$T_b$ : 90°C /  $T_m$ : 155°C /  $T_e$ : 160°C /  $T_g$ : 160°C

Screw speed: 250 [rpm]  
Injection time: 0.2 seconds  
Injection pressure: 1850 bar  
Cycle time: 8 seconds

The various gelatin compositions are moulded into capsule cap and body parts using a mould with eight cavities.

Under these conditions, gelatin capsules of good quality are obtained under continuous processing, - the capsule parts thus obtained are not soft and keep their shape unchanged upon storage.

Very good in vitro dissolution characteristics are obtained which are superior to those obtained from capsules produced without the addition of a disperse phase material.

### Example 3

Example 2 is repeated with a gelatin of 240 Bloom and a water content of 15 % by weight. To 100 parts of this gelatin 0.85 parts of the disperse phase materials and 0.5 parts of magnesium stearate are added and well mixed so that a free flowing granulate is obtained.

The processing conditions are as follows:

Barrel temperature profile:

$T_f$ : 90°C /  $T_m$ : 155°C /  $T_e$ : 160°C /  $T_g$ : 160°C

Screw speed: 250 [rpm]  
Injection time: 0.2 seconds  
Injection pressure: 1800 [bar]  
Cycle time: 8 seconds

The same mould is used as in Example 2. Under these conditions, and under continuous processing, precision gelatin capsules of

excellent quality are obtained. Capsule bodies are not soft and keep their shape unchanged upon storage.

Very good in vitro dissolution characteristics are obtained.

#### Example 4

100 parts of a commercial gelatin of 200 Bloom and with a water content of 12 % are mixed with 8 parts of glycerol and 1 part of disperse phase material (as in example 2) and the various gelatin mixtures are fed into an injection moulding machine to produce hard gelatin capsule body parts as described in Example 2.

The processing conditions are as follows:

Barrel temperature profile:

$T_f$ : 90°C /  $T_m$ : 120°C /  $T_e$ : 130°C /  $T_g$ : 130°C

Screw speed: 250 [rpm]

Injection time: 0.2 seconds

Injection pressure: 1500 [bar]

Cycle time: 8 seconds

The same mould is used as in Example 2. Under these conditions, and under continuous processing gelatin capsules of excellent quality and dissolution characteristics are obtained.

#### Example 5

100 parts of a commercial gelatin of 150 Bloom and a water content of 12 % are mixed with 10 parts of glycerol, 2 parts of disperse phase material (as in Example 1) and injection moulded to produce hard gelatin capsule parts as described in Example 3.

The processing conditions are as follows:

Barrel temperature profile:

$T_f$ : 90°C /  $T_m$ : 110°C /  $T_e$ : 120°C /  $T_g$ : 120°C

Screw speed: 250 [rpm]

Injection time: 0.2 seconds

Injection pressure: 1400 [bar]

Cycle time: 9 seconds

Under these conditions, and under continuous processing, gelatin capsules of excellent quality and dissolution characteristics are obtained.

#### Example 6

100 parts of a commercial gelatin of 150 Bloom and a water content of 12 % are fed into a twin screw extruder (Type Warner & Pfleiderer) at a rate of 5 kg/hour. At a separate inlet a 10 : 1 mixture of monoglycerinacetate and disperse phase material is fed into the extruder at a rate of 10 parts per hour. Temperatures are maintained at between 90°C and 105°C.

The solidified melt is granulated, from which granulate shaped articles are produced.

## CLAIMS

1. A composition capable of being formed into articles having substantial dimensional stability and improved dissolution characteristics, which composition comprises a medium and a phase, the medium functioning as a dispersion medium with respect to the phase, the phase functioning as a disperse phase with respect to the medium, the phase being present in the composition at a concentration sufficient to effect an increase in dissolution of articles in comparison with the rate of dissolution of articles made from a composition absent the phase, the medium comprising a solidified hydrophilic polymer and the phase comprising at least one hydrophilic material which is substantially insoluble in the medium comprising the hydrophilic polymer.

2. A composition according to claim 1, in which said hydrophilic material comprises a hygroscopic material.

3. A composition according to either of claims 1 or 2, in the form of a member selected from a powdery mixture of its components, a melt and a solidified form as obtainable from said melt.

4. A composition according to any preceding claim, in the form selected from a granulate, a pellet and a powder as obtained from a melt.

5. A composition claim, wherein the hydrophilic polymer is selected from:

substantially water-soluble polymers selected from animal gelatins, vegetable gelatins, sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, rape seed proteins, acrylated proteins; substantially water-soluble polysaccharides, alkylstarches, hydroxyalkyl starches and hydroxyalkylalkyl starches, starch esters and hydroxyalkyl starch esters; carboxyalkylstarches, carboxyalkylalkylstarches;

alkylcelluloses, hydroxyalkyl celluloses and hydroxyalkylalkyl celluloses, cellulose esters and hydroxyalkyl cellulose esters; carboxyalkylcelluloses, carboxyalkylalkylcelluloses and their alkali metal salts, polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinyl alcohols, polyvinyl acetatephthalates (PVAP), polycrotonic acids; polyitaconic acid, polymaleic acid; phthalated gelatin, crosslinked gelatin, shellac, gelatin succinate, cationically modified acrylates and methacrylates possessing a tertiary or quaternary amino group which may be quaternized, with the proviso that said polymer does not form a disperse phase.

6. A composition claim, wherein said hydrophilic polymer is gelatin.

7. A composition according to any one of claims 1 to 5, wherein said hydrophilic polymer is selected from methylstarch, hydroxymethylstarch, hydroxyethyl starch, hydroxypropyl starch, hydroxyethylmethyl starch, hydroxypropylmethyl starch, hydroxybutylmethyl starch, starchacetatephthalate and hydroxypropylmethyl-starch phthalate, methylcellulose, hydroxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose, and hydroxybutylmethyl cellulose, cellulose acetatephthalate and Hydroxypropylmethyl cellulose phthalate

8. A composition according to any preceding claim, which further comprises at least one other hydrophilic polymer added thereto in an amount of up to 50 % by weight based on the weight of the dry components of the composition.

9. A composition according to any preceding claim, wherein the water content is about 1 to 40 % by weight of the total composition.

10. A composition according to any preceding claim, wherein the hydrophilic material of the disperse phase has a melting point which is higher than the glass transition temperature of said hydrophilic polymer.

11. A composition according to any preceding claim, wherein said hydrophilic material absorbs water in an amount of up to 1,000 times its own weight.

12. A composition according to any preceding claim, wherein said hydrophilic material is present in said composition at a concentration of between 0.1 and 4 percent by weight, based on the weight of the composition, preferably at a concentration of between 0.1 and 2% by weight, based on the weight of the composition, more preferably at a concentration of between 0.3 and 2% by weight, based on the weight of the composition, and most preferably at a concentration of between 0.5 and 1.5% by weight, based on the weight of the composition.

13. A composition according to any preceding claim, wherein the hydrophilic material comprises a polysaccharide, selected from cellulose, chitin, chitosan and starch.

14. A composition according to claim 13, wherein the polysaccharide is substituted.

15. A composition according to claim 14 wherein the polysaccharide is substituted with a member selected from carboxy-, carboxyalkyl and salts thereof, sulfoalkyl- and salts thereof, dialkylaminoalkyl and quaternary derivatives thereof.

16. A composition according to any one of claims 13 to 15, in which the polysaccharide is selected from carboxymethyl cellulose, diethylaminoethyl cellulose, triethanolamine cellulose, polyethyleneimine cellulose and

carboxymethyl starch.

17. A composition according to any one of claims 13 to 16, in which the polysaccharide is stranded or fibrous and have a length of from 10 to 500um, preferably from 20 to 300um, and most preferably from 20 to 100um.

18. A composition according to any one of claims 13 to 17, wherein the polysaccharide is crosslinked.

19. A composition according to the preceding claim, wherein the polysaccharide is selected from cross-linked carboxymethyl starch, and salts thereof, internally cross linked carboxymethyl cellulose and salts thereof, and cellulose amines possessing tertiary or quaternary amino groups.

20. A composition according to claim 13, in which the polysaccharide is a pullulan or pullulan derivative.

21. A composition according to the preceding claim, in which the pullulan or derivative is substituted to a degree of between 0.5 and 1.2.

22. A composition according to any one of claims 1 to 12, wherein said hydrophilic material consists of internally cross linked polyvinylpyrrolidone or a salt thereof.

23. A composition according to any preceding claim, wherein said composition contains further additives including fillers, mould release agents, plasticizers, stabilizers and colouring agents.

24. Shaped finished articles as obtained from a composition capable of being formed into articles having substantial dimensional stability and improved dissolution characteristics, which composition comprises a medium and a



phase, the medium functioning as a dispersion medium with respect to the phase, the phase functioning as a disperse phase with respect to the medium, the phase being present in the composition at a concentration sufficient to effect an increase in dissolution of articles in comparison with the rate of dissolution of articles made from a composition absent the phase, the medium comprising solidified hydrophilic polymer and the phase comprising at least one hydrophilic material which is substantially insoluble in the medium comprising the hydrophilic polymer.

25. An article made from a composition as claimed in any one of claims 1 to 23.

26. An article according to claim 25, in the form of a pharmaceutical capsule.

27. A method of producing a composition - capable of being formed into articles having substantial dimensional stability and improved dissolution characteristics, which composition comprises a medium and a phase, the medium functioning as a dispersion medium with respect to the phase, the phase functioning as a disperse phase with respect to the medium, the phase being present in the composition at a concentration sufficient to effect an increase in dissolution of articles in comparison with the rate of dissolution of articles made from a composition absent the phase, the medium comprising solidified hydrophilic polymer and the phase comprising at least one hydrophilic material which is substantially insoluble in the medium comprising the hydrophilic polymer, which process comprises heating said hydrophilic polymer to a temperature above the melting point and glass transition temperature of the hydrophilic polymer for a time sufficient to effect deconstructurisation, characterised in that the material which functions as the disperse phase is added to the hydrophilic polymer either before, during or after melt formation.

28. A method according to the preceding claim, wherein the hydrophilic polymer is gelatin.

29. A method of shaping the composition of any one of claims 1 to 23, under controlled water and pressure conditions, which method is selected from moulding, blow moulding, extrusion, coextrusion, compression moulding, vacuum forming, thermoforming and foaming.

30. An article as obtained from the method claimed in claim 29.

31. A composition according to any preceding claim with reference to the accompanying examples.

**Patents Act 1977**  
**Examiner's report to the Comptroller under**  
**Section 17 (The Search Report)**

Application number

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**Relevant Technical fields**

(i) UK Cl (Edition K ) C3N

(ii) Int Cl (Edition 5 ) A61K C08J

Search Examiner

MR P BACK

**Databases (see over)**

(i) UK Patent Office

(ii) WPI

Date of Search

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Documents considered relevant following a search in respect of claims

1-31

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
X	GB 2148235 A (WARNER-LAMBERT)	1, 5, 6, 24, 27
X	GB 1405342 (NATIONAL STARCH)	1, 5, 6, 24, 27
X	EP 0374359 A2 (PHARMCAPS)	1, 5, 6, 24, 27
X	EP 0092908 (WARNER-LAMBERT)	1, 5, 6, 24, 27
X	WO 87/01034 (ANMELDER)	1, 5, 6, 24, 27
X	US 4987031 (SHIAZO)	1
X	US 4655840 (WARNER-LAMBERT)	1, 5, 6, 24, 27

Category	Identity of document and relevant passages	Relevant to claim(s)

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